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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/477,989	06/07/95	BAZIN H	61750-147

EXAMINER

18M1/1223

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ART UNIT	PAPER NUMBER
1806	14

DATE MAILED: 12/23/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/18/97

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 11-46 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 11-46 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 9/18/97 (Paper No. 12), is acknowledged.
Claims 1-10 have been canceled.
Claims 11-46 have been added.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments, filed 9/18/97 (Paper No. 12).
The rejections of record can be found in the previous Office Action (Paper No. 9).

3. Again, the communication filed 9/18/97 (Paper No. 12) like the communication filed on 2/28/97 (Paper No. 8) is not fully responsive to the communication mailed 3/18/97 and 11/2/96, respectively, for the reasons(s) set forth on the Notice to Comply with the Sequence Rules sent in Paper No. 9.

Again, Applicant is required to complete the response to this Office Action in the interest of compact prosecution,

3. The drawings submitted with this application were declared informal by the applicant. Accordingly, they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review.

4. Applicant's amendment, filed 9/18/97 (Paper No. 12), amended the specification to provide a Summary of the Invention to the instant application.

5. Claims 11-20, 27-34, 38-46 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed, that is, the recitation of amino acid substitutions in the human framework of antibodies other than the LO-CD2a antibody produced by the ATCC HB 1123 hybridoma.

Applicant has not provided appropriate blazemarks in the specification as-filed to support the "claimed limitations" indicated above. The instant specification discloses the particular amino acid substitutions currently claimed with respect to the particular embodiment of the LO-CD2a antibody (see page 15, paragraph 1 and Example 7). The specification as filed does not provide a written description or set forth guidance and direction to humanized antibodies and the use of said humanized antibodies wherein "said humanized antibodies binding to the same epitope of human lymphocytes as the monoclonal antibody produced by the cell line deposited as ATCC HB 11423". Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

6. Claims 11-20, 27-34 and 38-46 are rejected 35 U.S.C. § 112, first paragraph, because the specification while being enabling for providing for the particular amino acid substitutions for the particular LO-CD2a antibody does not reasonably provide enablement for the claimed amino acid substitutions in the human framework of antibodies other than the LO-CD2a antibody produced by the ATCC HB 1123 hybridoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant has not enabled the particular substitutions for any antibody binding the same epitope as the LO-CD2a antibody and maintain the properties of a functional humanized antibody either as a diagnostic or a therapeutic agent. An effective number of substituting amino acid residues in framework regions that are consistent with corresponding framework regions of a human antibody of one embodiment such as the LO-CD2a antibody does not necessarily correlate with making the same amino acid substitutions with any CD2-specific antibody and with any human immunoglobulin. Both CDRs and framework regions contribute to successful humanization of functional antibodies. Often excising out portions of a protein or modifications to a protein would result in deleterious effects to the overall activity and effectiveness of a protein. Applicant has not clearly shown or define the criticality or permissibility of the modifications encompassed by the claims that result in retaining the appropriate functional characteristics of said humanized antibody, commensurate in scope with claimed antibodies. Applicant has failed to enable a myriad of functional humanized CD2-specific antibodies and fails to provide clear guidance to those skilled in the art on how to make and use said humanized CD2-specific antibodies. One of the skill in the art would neither expect nor predict that the particular amino acid substitutions relied upon in generating the LO-CD2a antibody with HUM500 framework regions as set forth in Example 7 of the instant specification would result in the appropriate functioning of the humanized antibodies as broadly as is claimed. It appears that undue experimentation would be required of one skilled in the art to practice the claimed compositions and methods using the teaching of the specification alone.

7. Applicant's assurances, filed 9/18/97 (Paper No. 12), have obviated the previous rejection as it would apply to the instant claims under 35 U.S.C. § 112, first paragraph, for satisfying the deposit of biological materials.

8. Prior Art Rejections

A) Claims 11-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Xia et al. (Rat Hybridomas and Rat Monoclonal Antibodies, 1990; 1449) or Bombil et al. (Cancer Immunol. Immunother., 1995) in view of Queen et al. (U.S. Patent No. 5,530,101) essentially for the reasons of record set forth in the last Office Action (Paper No. 9.

B) Claims 27-46 are rejected under 35 U.S.C. § 103 as being unpatentable over Guckel et al. (J. Exp. Med., 1991; 1449), Bromberg et al. (Transplant., 1991; 1449), Hafler et al. (J. Immunol., 1988; 1449), Chavin et al. (Transplant., 1992; 1449), or Faustman (U.S. Patent No. 5,283,058) in view of Xia et al.(Rat Hybridomas and Rat Monoclonal Antibodies, 1990; 1449) or Bombil et al. (Cancer Immunol. Immunother., 1995) and Queen et al. (U.S. Patent No. 5,530,101) essentially for the reasons of record set forth in the last Office Action (Paper No.9).

9. Applicant's Arguments and the Examiner's Rebuttal to Prior Art Rejections

Applicant's arguments in conjunction with the White-Scharf declaration under 37 C.F.R. § 1.132, filed 9/18/97 (Paper Nos. 12-13) have been fully considered but are not found convincing.

A) Applicant argues that the reference does not disclose or define the characteristics that specifically identify the claimed antibody species LO-CD2a. In turn, applicant argues that if one skilled in the art is not enabled by Xia to obtain LO-CD2a antibody, the one skilled in the art is not enabled to produce a humanized form of such antibody. Applicant argues that Queen is broadly directed to humanized antibodies and contemplates framework substitutions, such generic disclosure alone or in combination with the other cited art is not sufficient to negate the patentability of the claimed antibodies which are directed to antibodies including a defined framework substitution in combination with defined CDRs. Applicant argues that Bombil does not enabled one skilled in the art to obtain LO-CD2a antibody, even though the article indicates that LO-CD2a was used. Applicant argues that the claims further define over the art of record in that none of the art or record specifically suggests substituting residues at the defined positions when the CDRs are obtained from an antibody which binds to the same epitope as LO-CD2a antibody. In addition, applicant also argues that even if the LO-CD2a antibody is enabled by the cited prior art (which it is not), the claims which are directed to antibodies with defined framework substitutions in combination with certain CDRs are patentable in that the claimed prior art alone or in combination does not disclose the portions of the donor antibody which should be substituted in the framework when using the defined CDRs.

In contrast to applicant's assertions, Xia et al. provides a number of phenotypic and functional characteristics that are associated with the LO-CD2a specificity (see entire document). Also, Xia et al. distinguishes the LO-CD2a specificity from other CD2-specific antibodies and clearly discloses that this specificity binds a different epitope from other CD2-specific antibodies (for example, see page 320, paragraphs 1-3). It would have been expected at the time the invention was made that different antibodies would recognize the same conformational epitope, which is the LO-CD2 epitope in the instant case. The prior art clearly set forth numerous features that characterize and enable one of skill in the art at the time the invention was made to make such a compound or antibody that binds to the same LO-CD2 epitope specificity as claimed. There is no objective evidence that the LO-CD2a specificity differs in any significant manner from the numerous characteristics given by the reference that distinguished the LO-CD2a specificity from other antibodies including other CD2-specific antibodies.

In addition, the biological material LO-CD2a antibody and hybridoma or specificity were referenced in Bombil, which indicates that this antibody was known and publicly available to others as disclosed. Applicant has not provided objective evidence that others did have the instant LO-CD2a antibody and hybridoma made available to them upon request.

As page 15, paragraph 1 of the instant specification acknowledges, a humanized antibody was constructed by replacing corresponding amino acids of the human framework with the noted amino acids from the corresponding murine antibody (e.g. rat LO-CD2a framework). This was standard practice at the time the invention was made, as evidenced by Queen et al. and acknowledged by applicant. Given the availability of the LO-CD2 antibody or the LO-CD2a antibody specificity in the prior art as well as the

standard practices of generating humanized antibodies by modifying the appropriate framework regions based upon the sequence homology or identity between the donor and acceptor immunoglobulins to retain specificity and functional properties of the native antibody; amino acid substitutions including the instant modification would have been obvious or expected at the time the invention was made. Also note that the claims rely upon "at least one" amino acid substitution, which also indicates that the nature and number of amino acid substitutions relies upon particular donor and acceptor immunoglobulins in generating a humanized antibody. Again, the prior art provides for the LO-CD2a antibody and antibodies that bind the LO-CD2a specificity. In addition to the Queen et al. patent itself, it is noted that the humanization of immunoglobulin according to the procedures of Queen et al. were commercialized at the time the invention was made.

As pointed out in the last Office Action, Queen et al. teach that the method of humanizing antibodies in order to reduce immunogenicity while retaining high binding affinity for diagnostic and therapeutic purposes as well as the appropriate vectors, host cells, etc. to accomplish the engineering of chimeric and humanized antibodies (see entire document). The determination and manipulation of the nucleic acid sequence is an outcome and mechanism of such engineering. Although Queen et al. do not teach humanizing the specific antibodies of the instant invention, however, one of ordinary skill in the art at the time the invention was made would have been motivated to do so for any antibody intended for various diagnostic and therapeutic use in humans for the reasons cited above in the previous section. Therefore, from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

It would have prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the LO-CD2a specificity taught by Xia et al. or Bombil et al. in the generally applicable immunoglobulin gene cloning methods taught by primary references in order to obtain DNAs encoding the heavy and light chain variable regions of the LO-CD2a specificity. Having obtained said DNAs it would have been obvious to insert them into suitable expression vectors to express the constructs. One of ordinary skill in the art would have been motivated to do so in view of the above teachings of the advantage of producing chimeric immunoglobulins for in vivo diagnostic and therapeutic regimens in humans to reduce their immunogenicity as well as to produce high level expression of immunoglobulins of interest. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

B) With respect to the method claims, applicant argues that method claims are patentable over the prior art for the reason that the prior art does not place those skilled in the art in possession of the compounds used in the claimed process. Further, applicant argues that ht prior art does not provide any reasonable expectation that the claimed antibodies could be successfully used in humans and asserts that the prior art as a whole suggest that CD2 antibodies would not be successful by pointing out the distinction between pages 40-43 of the instant specification and the prior art teachings of CD2-specific antibodies that were not successful in primates including humans..

Guckel et al., Bromberg et al., Hafler et al., Chavin et al. and Faustman all teach the art-known potent inhibition of immune responses against antigens in vivo by blocking or modulating T cell surface receptors such as CD2 that are important in adhesion receptor-signaling (see entire documents particularly the Introductions and Discussions). In addition to this combination of references, Bombil et al. clearly teach the use of the particular LO-CD2a antibody specificity to inhibit human T cells activation and engraftment in vivo. Therefore, the instant LO-CD2a specificity was shown to inhibit human inflammatory responses, including inhibiting in vivo functions. Applicant has not provided objective evidence why this Bombil et al. reference which relies upon the same antibody specificity as claimed would not have predicted.

Applicant states that in treating rejection or other T cell mediated response, it is virtually impossible to treat within 24 hours of antigen priming, thus the ability to treat patients successfully in accordance with the invention would not be expected.

This is not found convincing in that standard transplantation regimens rely on knowing when the transplant is administered (e.g. stimulus) and providing immunosuppression prior to, at the same time and after said transplantation.

Applicant states that is well-known in the art that antibodies function through their epitopes, the data indicates that the antibodies of the present invention may be employed for treating of patients. Because the prior art does not suggest the antibodies of the present invention, and since the prior art in fact would lead one skilled in the art to expect that CD2-specific antibodies could not be employed for treating of patients, the method claims are deemed patentable over the prior art. However, the prior art does provide for the LO-CD2a antibody or antibodies that bind the same epitope, as indicated above.

Applicant arguments are not found persuasive.

10. Claims 11-26 and 27-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application Serial Nos. 08/477,877 and 08/472,281, respectively. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to same or similar chimeric and humanized LO-CD2-specific antibodies and methods of use.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 11-26 and 27-46 are directed to an invention not patentably distinct from the claims of copending application Serial Nos. 08/477,877 and 08/472,281, respectively. Specifically, the conflicting claims are patentably distinct from each other because both applications are drawn to same or similar chimeric and humanized LO-CD2-specific antibodies and methods of use.

Commonly assigned 08/472,281 and 08/477,877, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Applicant's arguments in conjunction with the White-Scharf declaration under 37 C.F.R. § 1.132, filed 9/18/97 (Paper Nos. 12-13) have been fully considered but are not found convincing.

Applicant argues that in regarded to the potential rejection under 34 USC 102(f) or (g), the humanized form of the antibody, defined in the present application, patentably defines over the noted copending applications by defining donor residues which are substituted in the framework. Although the LO-CD2a antibody including humanized and chimeric forms thereof was invented by the applicant of the noted copending applications, the present application which includes additional inventions claims a patentably distinguishable invention by defining certain framework residues which are substituted from the donor antibody in the human framework. The substitutions of such defined residues is not rendered obvious by the prior work of the names inventions of the noted copending applications.

Although the disclosures of the copending applications are identical, the subject with respect to defined substitutions in the human frameworks was the joint invention of the applicants of the present application. Since copending applications do not specifically claim the defined substitutions and since the defined substitutions is a joint invention of the inventors of the present applications, which is patentably distinguishable from LO-CD2a antibody and a generic invention of a humanized form thereof, there is no conflict between the claims of the present application and those of the noted copending applications.

In contrast to applicant's assertions, the defined substitutions do not defined the instant claims over either the same LO-CD2a specificity or humanized LO-CD2a specificity for the reasons of record and reiterated above in section 9. Furthermore, the same LO-CD2a antibody including the same defined substitutions were disclosed by another in copending USSNs 08/472,281 and 08/477,877; therefore it appears that the inventors of USSNs 08/472,281 and 08/477,877 invented d and reduced to practice the claimed LO-CD2a, humanized LO-CD2a and humanized LO-CD2a with the instantly defined substitution. Applicant has not provided any objective evidence to indicate otherwise.

Applicant is required to address the issues in italics above.
Applicant's arguments are not found persuasive.

11. No claim is allowed.

12. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
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December 22, 1997

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